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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/842,469	04/26/2001	Leonard Buckbinder	pc10873B	7996

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EXAMINER	
MOORE, WILLIAM W	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 04/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/842,469	BUCKBINDER ET AL.	
	Examiner	Art Unit	
	William W. Moore	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14 and 19-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14 and 19-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 15, 2004, has been entered and Applicant's amendment of page 1 of the specification overcomes the objection of record to the specification and the amendments to claims 19-23 and 30-34 submitted January 15, 2004, avoid the rejection of record of claims 14, 19-23 and 25-39 herein under 35 U.S.C. § 102(e) over the published U.S. Patent Application No. 2002/0107361 of Heller et al. New grounds of rejection are stated herein, thus this action is not a final communication.

Claim Rejections - 35 USC § 101

35 U.S.C. § 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 14 and 19-39 remain rejected for reasons of record under 35 U.S.C. § 101 because the claimed invention lacks patentable utility.

Applicant's arguments filed January 15, 2004, have been fully considered but they are not persuasive. Applicant proposes at pages 8-12 in Remarks filed January 15, 2004, that the ADAMTS-E metalloprotease having the amino acid sequence set forth in SEQ ID NO:2 herein should be considered to have a specific and substantial activity as an aggrecanase because it "is a member of the family of proteins known as ADAMTS proteins", which "exhibit(s) characteristics of the well-characterized ADAM family of metalloproteases". Applicant argues that the "metalloprotease domain alignment" of the

specification's Figure 4 can be considered to place the ADAMTS-E within the ADAMTS family of ADAM metalloproteases generally and alleges that all family members "have the ability to degrade aggrecan" and suggests that, based on activities alleged to extend to all family members could allow the artisan to "imput[e] utility to the protein of the present invention". Yet a claimed invention must posses a specific, substantial and credible *in vitro* or *in vivo* utility and nothing in the record shows that all, or a majority, of the members of the ADAMTS family, or the members of the larger ADAM family, share a common activity with a common substrate and nothing in the record shows that the human ADAMTS-E amino acid sequence of SEQ ID NO:2 herein acts on any of the diverse substrates recognized by some family members such as aggrecan, brevican or collagen. The significant degree of sequence similarity the ADAMTS-E polypeptide shares with other mammalian ADAMTS metalloproteases suggests that it is also a metalloprotease but establishes no utility specific to the disclosed ADAMTS-E amino acid sequence of SEQ ID NO:2. Because the specification fails to identify a **specific** and substantial utility for the disclosed ADAMTS-E having the amino acid sequence of SEQ ID NO:2 herein described by claim 24, it cannot support a specific utility for the various, undisclosed, divergent genera of molecules described by claims 19-23 and 25-39, or the method of claim 14, at the time the application was filed.

That the record demonstrates no specific utility for the disclosed, native, ADAMTS-E polypeptide, that the great majority of the ADAM polypeptides discovered to date have no established substrate yet, and that no correlation, rigorous or otherwise, between metalloprotease amino acid sequences will permit the artisan to assume that a specific utility established for one member of this diverse family is shared by another are the factual findings and the evidence supporting the reasoning that products of claims 14 and 19-39 lack a specific utility. No credible assertion of a specific utility can be made

for even the native ADAMTS-E polypeptide having the amino acid sequence set forth in SEQ ID NO:2 where neither Applicant herein nor others in the prior art can identify the sequence characteristics of ADAM family members that confer substrate specificities on those few for which a substrate has been determined. A method of use of a material for further research to determine, e.g., its specific biological role, thus identifying or confirming a "real world" context for its use, cannot be considered to be a "substantial utility". *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966). Mere allegations of a prospective, potential, utility cannot rise to the level of a credible assertion of a **specific** *in vivo* utility that is substantial and mere sequence similarity cannot support a **specific** *in vitro* utility that is substantial.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14 and 19-39 also rejected under 35 U.S.C. §112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or a credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicant's arguments filed January 15, 2004, have been fully considered but they are not persuasive. Applicant suggests at pages 12-13 in Remarks filed January 15, 2004, that claim amendments describing narrower genera of divergent metalloproteases in new claims 19-23 and 25-39 are adequate to overcome the rejection of record. Since the disclosed amino acid sequence of SEQ ID NO:2, described by claim 24 is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to **use** this claimed invention or the various, undisclosed, members of the divergent genera described by

claims 19-23 and 25-30 or know how to usefully practice a method of claim 14, whether it depended from claim 19 or from claim 24.

Claims 14, 19-23 and 25-39 remain rejected for reasons of record under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant's arguments filed January 15, 2004, have been fully considered but they are not persuasive. Applicant suggests, at page 13 in Remarks filed January 15, 2004, that because the amendments describe narrower genera of divergent metalloproteases, claims 14, 19-23 and 25-39 need no longer be subject to the rejection of record. The rejection of record is maintained because the specification fails to exemplify or describe the preparation of the subject matters of divergent ADAMTS-E polypeptides of claims 19-23 and 25-39 or a method of use the divergent ADAMTS-E polypeptides of claim 19 according to claim 14. Indeed, where the specification discloses no specific substrate for the native ADAMTS-E product, there can be no disclosure of a method of claim 14 for identifying compounds which inhibit or "stimulate" the unknown proteolytic activity of the native ADAMTS-E having the amino acid sequence set forth in SEQ ID NO:2. Claims 19-23 and 25-39 remain drawn to genera of variant polypeptides having metalloprotease domains that differ from the 387-amino acid metalloprotease domain of SEQ ID NO:2 herein at as many as 38 amino acid positions in claim 19, at as many 19 positions in claim 20, at as many as 4 positions in claim 22, and while identical within this domain in claim 23 a variant polypeptide may still differ anywhere within the region of the prodomain in claims 19-23, and 25-29, and may still differ at equivalent numbers of other amino acid positions elsewhere throughout the remaining 717 amino acids beyond the metalloprotease domain in claims 19-23 and 25-39.

Applicant's argument at page 13 of the Remarks filed January 15, 2004, implies that statistical proposals should take the place of actual disclosures of **where** differences in the amino acid sequence of SEQ ID NO:2 might occur and **what** such differences might be. Statistical suggestions cannot compensate for a lack of disclosure of those amino acid sequence characteristics that make the ADAMTS-E product distinct from other metalloproteases and the specification does not otherwise disclose or suggest the nature or source of the claimed generic products. "While one does not need to have carried out one's invention before filing a patent application, one does need to be able to describe that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. §112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). Like claims invalidated in *University of California v. Eli Lilly*, claims 14, 19-23, and 25-39 rejected herein are designed to embrace other, as yet unknown, human and mammalian polypeptides, but "relevant identifying characteristic[s]" must describe a claimed invention so that the public could know that the inventor possessed the invention at the time an application for patent was filed, rather than suggestions of a "result that one might achieve if one had made that invention". *University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Nothing demonstrates that, at the time the specification was filed, Applicant was "able to envision" enough of the structure of any of these undisclosed generic proteins to provide the public with identifying "characteristics [that] sufficiently distinguish it . . . from other materials". *Fiers*, 25 USPQ2d at 1604 (citing *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).

Claims 14, 19-23 and 25-39 remain rejected for reasons of record under 35 U.S.C. §112, first paragraph, because the specification is not enabling for embodiments of a metalloprotease having an amino acid sequence wherein a metalloprotease domain diverges that present in the amino acid sequence of SEQ ID NO:2 by amino acid substitutions, deletions and insertions, or combinations thereof at as many as 38 amino acid positions, or even 4 amino acid positions within the metalloprotease domain and

differs by equivalent numbers of amino acid positions elsewhere. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to **make** the invention commensurate in scope with these claims.

Applicant's arguments filed January 15, 2004, have been fully considered but they are not persuasive in addressing the rejection of record for lack of enablement as to making the divergent products embraced by claims 19-23 and 25-39 and practicing an assay of claim with the divergent products. Applicant suggests at page 14 in Remarks filed January 15, 2004, that the claim amendments describing narrower genera of divergent metalloproteases in new claims 19-23 and 25-39 are adequate to overcome the rejection of record where "activities of the various domains" are imputed on the basis of an overall, albeit median, degree of sequence similarity with other ADAM family members. The rejection of record for lack of enablement as to making is maintained because claims 19-23 and 25-39 contemplate arbitrary amino acid substitutions, additions or deletions in multiple genera of products having as many 38 amino acid positions altered in claim 19, as many 19 positions altered in claim 20, at as many as 4 positions altered in claim 22, and, even where a product has an identical metalloprotease domain in claim 23, it may still differ anywhere within the region of the prodomain in claims 19-23, and 25-29, and may still differ at equivalent numbers of other amino acid positions elsewhere throughout the remaining 717 amino acids beyond the metalloprotease domain in claims 19-23 and 25-39. Because the degree of sequence divergence among ADAM metalloproteases is substantial, because few among them have had substrates identified, and because no particular function of an ADAMTS-E protease can be determined with which to practice an assay of claim 14, no one can know how many, and which, amino acid sequence alterations will abolish the activity of a divergent product. The specification cannot support introduction of even a few amino acid insertions, deletions, or substitutions in the amino acid sequence of SEQ ID NO:2, because it does not teach where these alterations may occur anywhere,

in any combination or any pattern, in the amino acid sequence set forth in SEQ ID NO:2. Neither the prior art made of record herewith nor in Applicant's Information Disclosure of Paper No. 6 can identify, taken together with the specification, a few amino acids in the primary sequences of members of the family of human ADAMTS metalloproteases that might be altered, nor teach the nature of an alteration that may be made, which permits a resulting polypeptide to support its native function. Mere sequence perturbation cannot enable the design and preparation of divergent metalloproteases to provide the public with products that retain the as yet unknown native function of the native ADAMTS-E.

It is well settled that 35 U.S.C. §112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. §112, first paragraph, for non-enablement. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (recognizing and applying the "*Forman*" factors). Cf., *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986) (citing eight factors relevant to analysis of enablement). The standard set by the CCPA, the precursor of the Court of Appeals for the Federal Circuit, is not to "make and screen" any and all possible alterations because a reasonable correlation must exist between the scope asserted in the claimed subject matter and the scope of guidance the specification provides. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 25 (CCPA 1970). The Federal Circuit approved the standard set by the CCPA in *Genentech, Inc. v. Novo-Nordisk A/S*, 42 USPQ2d 1001 (Fed. Cir. 1997). The scope of subject matters embraced by claims 19-23 and 25-39 is unsupported by the present specification even if taken in combination with teachings available in the prior art, therefore the rejection of record is sustained.

Claim 14 is separately rejected, in a new ground of rejection, because there is no enablement in the specification or prior art of record for assays to identify stimulators of metalloprotease activity even if an assay were to be conducted with the ADAMTS-E metalloprotease having the amino acid sequence set forth in SEQ ID NO:2. This basis for rejection is independent of the rejection for lack of enablement as to use set forth above based on the lack of a disclosure of a specific utility, and the lack of a credible utility, for the ADAMTS-E metalloprotease having the amino acid sequence set forth in SEQ ID NO:2. Even if the native ADAMTS-E protease were to have an utility, neither the specification nor the prior art of record herein can identify, or even suggest, a class of compound that might be employed in an assay to identify a stimulator of metalloprotease activity. In the absence of any guidance as to where to start the search for prospective stimulators, a method for identifying stimulators embraced by claim 14 cannot be considered to be enabled.

The following is a quotation of the second paragraph of 35 U.S.C. §112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14, 19-23 and 25-39 rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 14, 19-23 and 25-39 are indefinite because claims 19-23 and 25-39 fail to indicate the amino acid positions within SEQ ID NO:2 which are intended as boundaries for the "metalloproteinase domain", "disintegrin domain", "thrombospondin domain", and "prodomain". Failure to identify where the different measures of identity and nonidentity should be applied in the amino acid sequence of SEQ ID NO:2 is a failure to establish the metes and bounds of the claimed subject matter where the several domains indicated in the claim account for a little over half of the entire 1,011 amino acid sequence set forth in SEQ ID NO:2 and the specification indicates that more than one

"thrombospondin motif" is present within the sequence of SEQ ID NO:2. Claim 14 is further indefinite because clause (b) of the claim fails to identify which activity of an ADAMTS-E is to be measured and how it is to be measured.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is now 571.272.0933. The examiner can normally be reached between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can now be reached at 571.272.0928. The fax phone numbers for all communications for the organization where this application or proceeding is assigned remains 703.872.9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is now 571.272.1600.

William W. Moore
April 16, 2004

NASHAAT T. NASHED PHD.
PRIMARY EXAMINER